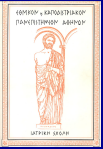


Sunitinib Induced Hypocalcaemia During Treatment of Pancreatic Neuroendocrine Tumours

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Aim of Study

Describe the development of hypocalcaemia as a potential adverse side effect in patients with neuroendocrine tumors (NETs) treated with sunitinib

Evaluate the potential beneficial effect of sunitinib in patients with refractory hypercalcaemia

Introduction

Sunitinib has been approved for the treatment of pancreatic NETs (pNETs)

Sunitinib

- Orally administered multi-targeted tyrosine kinase inhibitor
- Hypocalcemia is a reported adverse side effect described in the literature
- 35% suffer an adverse reaction to the drug
- No reports have been claimed in patients with pNETs

Refractory hypercalcaemia

- A relatively common paraneoplastic manifestation affecting 5% of patients with malignancies.
- Results mainly from the hypersecretion of PTHrP
- Diagnosis confirmed through elevated levels of PTHrP serum and undetectable levels of PTH

Cases Illustration

3 of 12 patients with pNETs treated with sunitinib developed hypocalcaemia

Case 1: A 51-year-old man

- Stage IV, grade 1 non-functioning pNET
- Disease progression despite treatment with somatostatin analogues (SA)
- Administered sunitinib since suffered a melanoma in the past

Case 2: A 53-year-old man

- Hyperparathyroidism requiring two resections
- 10 years later, diagnosed with MEN-1 and a stage IV, grade 1 non functioning pNET
- Initially treated with SA
- Recurrence ⇒ switched to everolimus: discontinued due to severe anemia

Case 3: A 58-year-old man

- Stage IV, grade 2 initially functioning pNET
- Developed severe and refractory hypercalcaemia due to PTHrP secretion
- Patient denied surgery which led to a selective chemoembolization of the hepatic artery
- Calcium controlled

Results

Table 1: Patients Grade of Hypocalcaemia

Case #	Time to Occurrence (months)	Toxicity Grade*	Calcium Level (mg/dL)**
1	9	2	7.1 (8.0-7.0)
2	6	1	8.0 (LLN-8.0)
3	1	4	6.0 (<6)

*All toxicities were reported according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

** Calcium levels are corrected for hypoalbuminemia

Case 3: Refractory Hypercalcaemia with Sunitinib

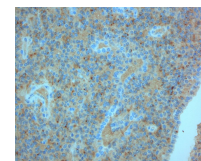


Figure 1: (+) Staining with chromogranin

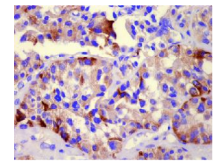


Figure 2: (+) Testing for PTHrP

Testing results confirm the neuroendocrine nature of the tumour and its high content in PTHrP

Calcium levels were reported above normal limits at [Ca 2.95 mmol / L (2.15 to 2.50)] and [Ca ** 1.43 mmol / L (1.00 to 1.30)] initially and then corrected

After developing grade 4 toxicity and reinstatement of previous treatment before sunitinib the refractory hypocalcaemia became easily controlled

Discussion

Hypocalcaemia is a possible adverse reaction to the agent

These cases are the first to report hypocalcaemia in patients with pNETs treated with sunitinib suggesting that this drug could be used in patients with refractory hypercalcaemia

Possible underlying mechanisms:

- Sunitinib could decrease elevated levels of PTHrP by direct antitumoral effect
- Sunitinib may interfere with the pathway of signal transduction through calcium sensor receptor

Conclusions

When patients who have pNET are treated with sunitinib, regular and frequent follow-ups assessing calcium levels should be performed

Hypocalcaemia as a side effect of sunitinib may be of therapeutic significance in patients who suffer from refractory hypercalcaemia due to hypersecretion of PTHrP by the tumor

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